

REMARKS

Claims 4-11 are currently pending in this application. Claims 4-6, 10, and 11 have been amended. Claims 13-25 have been added.

After entry of the above amendment, claims 4-25 will be pending. Claim 4 has been amended to be specifically drawn to the hybrid oligonucleotides of the invention. This amendment to claim 4 adds no new matter. Support for the amendment to claim 4 can be found, for example, at page 3, lines 24-33. Claims 5, 6, 10 and 11 have been amended to correct certain typographical errors and omissions. These amendments add no new matter and are supported by the application as filed. New claim 15 has been added, and is specifically drawn to the inverted hybrid oligonucleotides of the invention. New claim 15 adds no new matter. Support for new claim 15 can be found, for example, at page 4, lines 1-10. New claims 16-22, which all depend from new claim 15, have also been added. New claims 16-22 add no new matter. Support for new claims 16-22 can be found, for example, in pending claims 5-11. New claims 12-14 and 23-25 have also been added. These claims add no new matter. Support for new claims 12-14 and 23-25 can be found, for example, at page 8, lines 17-24. Applicants respectfully reserve the right to pursue subject matter given up with this amendment at a later date.

Double Patenting

Claims 4-11 continue to stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/291,058. The Examiner has acknowledged that the provisional obviousness-type double patenting rejection will be withdrawn when it is the only remaining rejection, but that maintenance of the provisional rejection is appropriate until such time.

To the extent that this same provisional obviousness-type double patenting is to be applied to the instantly presented claims, which include amended claims 4-6, 10 and 11, as well as new claims 12-24, Applicants respectfully request that this provisional obviousness-type double patenting rejection continue to be held in abeyance until a finding of allowable subject matter has been made in this or the cited application (*i.e.*, U.S. Ser. No. 10/291,058).

Rejection under 35 U.S.C. §103

The Office Action states that claims 4-11 continue to be rejected under 35 U.S.C. §103(a) as being unpatentable over Metelev *et al.* (U.S. Patent No. 6,143,881) in combination with Ghosh *et al.* ((1993) Anti-Cancer Drug Design 8(1): 15-32). In particular, the Office Action states that “it would have been obvious to one of ordinary skill in the art to make a hybrid oligonucleotide comprising a region of alternating phosphorothioate and phosphodiester linkages, as taught by Ghosh *et al.*, with a region of 2’-O-substituted ribonucleotides, as taught by Metelev *et al.*... (and that)... Metelev *et al.* provide a motivation to do so, teaching that hybrid oligonucleotides comprising phosphorothioate and phosphodiester linkages and 2’-O-substituted ribonucleotides and deoxyribonucleotide regions have superior properties of duplex formation, RNase H activation and nuclease resistance when used as an antisense molecule.”

First, independent claim 4 has been amended to specifically claim a hybrid oligonucleotide that includes one or more deoxyribonucleotide POPS blocks that are flanked by regions of at least two contiguous 2’-O-substituted ribonucleosides. Similarly, new independent claim 15 has been added to specifically claim an inverted hybrid oligonucleotide that includes one or more regions of 2’-O-substituted ribonucleosides that are flanked by regions of deoxyribonucleoside POPS blocks. Applicants respectfully note that the rejection of record does not address the presently-claimed, positionally-restricted POPS block(s)/2’-O-substituted ribonucleoside oligonucleotide compositions.

Second, Applicants note that the Office Action continues to reason that “since each of Metelev *et al.* and Ghosh *et al.* teach oligonucleotides having increased nuclease resistance they do share a common purpose that would make their combination to produce new oligonucleotides also having the same property of increased nuclease resistance obvious to the person of ordinary skill in the art.” However, Applicants respectfully note that this same reasoning was earlier presented in this case by the previous Examiner, who relied upon MPEP 2144.06 and the ruling in *In re Kerkhoven* (626 F.2d 846 (CCPA 1980)). In response, Applicants asserted, and continue to assert here, that the holding in that case is not governing in the instant application. In particular, the holding in *In re Kerkhoven* states that “it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose” (emphasis added) (*In re Kerkhoven*, 626 F.2d 846 (CCPA 1980)). The “two compositions” that were combined in

Kerkhoven were “two conventional spray-dried detergent compositions”. In contrast, the instant invention involves two types of chemical modifications in a single covalent composition. The predictability of properties resulting from the combination of two types of chemical modifications into a single, covalently-joined (oligonucleotide) molecule is considerably less than that of the predictability of properties resulting from the combination of two known separate and distinct (detergent) molecules. Furthermore, the field of art in *Kerkhoven*, related to chemical detergents, is far simpler and more predictable than that of Applicant’s invention, which relates to a biologically active antisense oligonucleotides that interact *in vivo* with specific biological targets.

Therefore, Applicants respectfully assert that a proper inquiry into obviousness must necessarily respect the highly factual nature of the analysis, which is based upon the knowledge and understanding of one of skill in the art (see *Graham v. John Deere Co.* 383 U.S. 1 (1966)). Accordingly, the technical field involved in general, and the technical features of the claimed invention in particular, necessarily weigh heavily in the determination, and so it would be clearly improper to ignore these factors in relying upon a holding (*In re Kerkhoven*) that is clearly inapplicable to the facts in the instant invention.

Third, notwithstanding the fact that Applicants believe that there continues to be no showing of *prima facie* obviousness, Applicants are submitting herewith the Declaration of Dr. Ekambar R. Kandimalla, which attests to the lack of motivation of one of skill in the art to combine the Ghosh *et al.* and Metelev *et al.* references to arrive at the instantly claimed invention. In particular, Dr. Kandimalla was a person of skill in the art at the time of the invention, and his sworn statement supports the fact that motivation to combine the cited references at the time of the invention was lacking. Furthermore, Applicants note that the Examiner has not addressed their previously-asserted argument that the co-inventor Agrawal’s actual knowledge, as a co-inventor of the Metelev *et al.* invention, did not lead to the instant invention until a later time prior to the filing of the instant invention. In particular, the Office Action states that this argument is “circumstantial evidence”, and, since it is not supported by a sworn affidavit, it has not been considered and addressed. Accordingly, the Declaration of Dr. Ekambar R. Kandimalla includes a statement on this point of actual knowledge of the cited references by a skilled artisan. Appropriate weighting of this evidence, and reconsideration of the *prima facie* case for obviousness is therefore respectfully requested.

Fourth, Dr. Kandimalla's Declaration supports the fact that, even supposing such motivation to combine had existed at the time of the invention, there was still no reasonable expectation of success in so combining the claimed features. Relevant to this point, Applicants further note that the Office Action summarily concludes "one of skill in the art would have had a reasonable expectation of success in combining the teachings of Metelev et al and Ghosh et al. because the ability to synthesize oligonucleotides containing 2'-O-substituted sugars and both phosphorothioate phosphodiester linkages and in any pattern was routine in the art at the time of invention" (emphasis added). However, it is not the ability to synthesize, or make, but rather the ability to use that clouds the skilled artisans expectation of success in this instance. Accordingly, Dr. Kandimalla's Declaration addresses this point as well. Further appropriate reconsideration of the *prima facie* case for obviousness in view of this evidence is therefore respectfully requested.

Finally, Applicants note that their prior arguments regarding unexpected results have not been fully considered and weighted because they "do not appear in the prior art or in a sworn declaration and hence cannot be adequately answered." Accordingly, the Declaration of Dr. Ekambar R. Kandimalla still further includes a statement on this data and its significance to one of skill in the art at the time of the invention. Appropriate reconsideration of this evidence of nonobviousness is further respectfully requested.

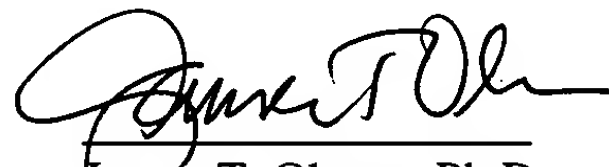
In conclusion, reconsideration and withdrawal of the rejection under 35 U.S.C. §103 in view of Metelev *et al.* and Ghosh *et al.* is respectfully requested in view of the amended claims, further in view of the inapplicability of *In re Kerkhoven*, and still further in view of the Declaration under 37 C.F. R. 1.132 of Dr. Kandimalla, which attests to both the lack of motivation to combine the cited references and lack of a reasonable expectation of success in so doing, as well as to the existence of unexpected results in the properties of the claimed compositions.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

The time for responding to this action has been extended to September 2, 2005 by the accompanying Petition for a Three Month Extension of Time and payment of fee. Applicants believe no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,



James T. Olesen, Ph.D.
Attorney for Applicant
Reg. No.: 46, 967

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Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000